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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/824,627	04/14/2004	Renata Pasqualini	UTSC:858US	6275

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EXAMINER	
POPA, ILEANA	
ART UNIT	**PAPER NUMBER**
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/824,627	PASQUALINI ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-35,37,38,40 and 41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-35,37,38,40 and 41* is/are rejected.

7)☒ Claim(s) *26-35, 37, and 38* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5)☐ Notice of Informal Patent Application
6)☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office action.

2. Claims 1-25, 36, and 39 have been cancelled. Claims 40 and 41 are new. Claims 26-35, 37, 38, 40, and 41 are pending and under examination.

3. All rejections pertaining to claims 25 and 36 are moot because Applicant cancelled the claims in the response filed on 09/18/2007.

Response to Arguments

Claim Rejections - 35 USC § 112, enablement

4. Claims 26-35, 37, and 38 remain and the new claims 40 and 41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for the reasons of record set forth in the non-final Office action of 06/18/2007. Applicant's arguments filed 09/18/2007 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that Example 1 in the specification demonstrates the successful *in vitro* immunization of spleen cells and their subsequent immortalization without forming hybridoma. Consequently, Applicant asserts that the Examiner was wrong in making the enablement rejection because immunization can take place *in vitro* (see the non-final Office action of 06/18/2007).

It is noted that Example 1 does not disclose convincing data because the splenocytes used *in vitro* were derived from mice immunized with the antigen, and therefore, what happens *in vitro* is just activating splenocytes already primed *in vivo* (i.e., immunized *in vivo*). Applicant did not provide any evidence that the splenocytes used in Example 1 were derived from a mouse that was not exposed to the antigen. One of skill in the art would not recognize that such data demonstrates immunization *in vitro*. Therefore, the rejection is maintained.

Claim Rejections - 35 USC § 103

5. Claims 25-35, 37, 38 remain and the new claims 40 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Green (J Immunol Meth, 1999, 231: 11-23, of record), in view of both Kano (JP62195296, of record), Jat et al. (Proc Natl Acad Sci USA, 1991, 88: 5096-5100, of record), and Lidington et al. (Am J Physiol Cell Physiol, 2002, 282: C67-C74) for the reasons of record set forth in the non-final Office action of 06/18/2007. Applicant's arguments filed 09/18/2007 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that Green teaches Xenomouse, i.e., a mouse capable of producing human antibodies, and wherein the Xenomouse is to be used in obtaining human monoclonal antibodies via the established hybridoma production, i.e., Green's Xenomouse is incapable of producing immortalized antigen-producing cells without forming hybridomas. Therefore, Applicant argues, Green teaches away from the claimed invention. With respect to Kano, Applicant

argues that the reference specifically teach *ex vivo* introducing of the immortalizing oncogene into spleen cells obtained from immunized rabbits, which is contrary to the claimed invention wherein the spleen cells will inherently have the capability to be immortal without *ex vivo* introduction of an oncogene. With respect to Jat et al., Applicant argues that the reference provides no suggestion, motivation, or reasonable expectation of success that a mouse as claimed could even be obtained. Applicant submits that Jat et al. teach only few cell types from their Immortomouse, such as skin fibroblasts and thymic epithelial cells, without disclosing antibody producing cells. Therefore, Applicant argues, since Jat et al. are silent with respect to antibody producing cells, there is no reason that one of skill in the art would choose to genetically engineer an Immortomouse to incorporate human antibody genes. Applicant asserts that Jat et al. teach that there is a high degree of uncertainty regarding the ability to immortalize individual cell types from such a mouse (paragraph bridging p. 5099 and 5100, p. 5100, first paragraph, and the final paragraph). With respect to Lidington et al., Applicant argues that the reference is not relevant because the reference is drawn to immortalization of growth factor-responsive endothelial cells and says nothing about crossing to introduce a human antibody genetic background or the preparation of immortalized antibody-producing cells. Applicant asserts that one of skill in the art would not have had a reasonable expectation of success in obtaining a mouse that stably contains the genetic background for the production of human antibodies and for immortalization or successfully immortalize antibody-producing cells, much less antibody producing cells that contain transgenic human genes for antibody production.

In support of this assertion, Applicant encloses the declaration of the inventors, which provides evidence that one of skill in the art would have no reasonable expectation that immortalization of splenocytes obtained from mice having the genetic components of the human antibodies as well as the genetic component for immortalization would be successful. In the declaration, Applicant states that in order to maintain the cells from a mouse comprising the temperature-sensitive SV40 large T (tsSV40Tag), cells must be maintained at 33° C and it is not a given this would allow for the successful expansion and selection of splenocytes secreting monoclonal antibodies of interest at sufficient amounts, since splenocytes that do not produce the monoclonal antibodies would grow faster and take over the culture; such a concern was raised by a scientific reviewer who evaluated Applicant's manuscript that describes the instant invention. In the declaration, Applicant also states that, as pointed out by the reviewer, it was expected that, even if obtained, the cloning of monoclonal antibody-secreting cells would not be possible due to their rarity and inability to grow within the constraints of limiting dilution; surprisingly, this turned out not to be true in the instant case, since the tsSV40Tag spleen cell mixtures were found to provide an ideal system for single cell cloning, due to the presence of other immortalized cells, such as macrophages, stromal cells, or endothelial cells) that apparently serve as feeder layer. Therefore, Applicant argues, one of skill in the art, as exemplified by the reviewer, would not have had an *a priori* expectation that the claimed invention would work and Applicant's achievement is surprising, as indicated by the reviewer. Therefore, Applicant argues, a *prima facie* case of obviousness has not been established and the rejection should be withdrawn.

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Just because Green teaches using hybridoma to immortalize the antibody-producing cells obtained from their Xenomouse does not mean that they teach away from the invention, since they do not teach or even suggest that other immortalization methods would not work with their cells, i.e., their splenocytes would not be prone to immortalization by oncogenes such as tsSVTag. On the contrary, the art clearly teaches the successful use of oncogenes to immortalize splenocytes. For example, Kano teaches monoclonal antibody production without using hybridoma formation by using SV40Tag to immortalize antigen-primed splenocytes for the production of stable monoclonal antibody-producing B-cells (Abstract, p. 6, first and second paragraphs; a copy of the English translation of Kano is hereby provided). Clearly the prior art teaches direct immortalization of B-cells using oncogenes such as the SV40 T antigen (SV49Tag) as an alternative approach to generate immortalized B-cell lines for the production of monoclonal antibodies. Therefore, one of skill in the art would have known to modify Green's method by replacing the time-consuming immortalization by hybridoma formation with Kano's simpler procedure , i.e., *ex vivo* immortalization with SV40Tag (claim 40). Jat et al. teach that immortalization *ex vivo* is complex and

unpredictable and that the use of Immortomouse (i.e., a mouse harboring ts58A in its genome) overcomes the disadvantages of *ex vivo* immortalization because it facilitates and it ensures the presence of the conditional oncogene in all cells, at a common integration site and therefore, consistent derivatization of cell lines with the same characteristics (p. 5096, column 1 and 2, p. 5100, column 1 last paragraph). Lidington et al. teach that, similar to the wild type SV40Tag, tsSV40Tag could also be used to immortalize cells. The argument that the Lidington et al. reference is irrelevant because the reference teaches immortalization of endothelial cells and says nothing about crossing mice to introduce a human antibody genetic background or about the preparation of immortalized antibody-producing cells is not found persuasive. The reference was cited and it is relevant because it teaches the advantages using tsSV40Tag versus SV40Tag and the advantage of using the Immortomouse (i.e., tsSV40Tag transgenic mice) to obtain diverse immortalized cell lines, beside the endothelial cell lines. By reading the above references, one of skill in the art would have known and be motivated to use the Immortomouse to obtain monoclonal antibodies in the absence of hybridoma formation. In addition to the above, Lidington et al. teach crossing the Immortomouse with other genetically modified mice to obtain immortalized cells with a desired genetic background (Abstract, p. C67, column 2, first full paragraph, p. C72, column 1, p. C73, paragraph bridging p. C74, p. C74, column 1). It is noted that Lidington et al. reference is not the only prior art to suggest crossing the Immortomouse with genetically modified mice. For example, Noble et al. (Transgenic Research, 1995, 4: 215-225, Abstract) teach generation of cell lines from offspring of

crosses between the Immortomouse and mutant mice of interest (Abstract). Based on all the teachings above, one of skill in the art would have known to immortalize cells from any genetically altered mouse (including the Green's Xenomouse) by introducing the tsSV40Tag into the genetic background of the genetically altered mouse via crossing the mouse with the Immortomouse (claim 41). With respect to crossing the Immortomouse with Green's Xenomouse, one of skill in the art would have been motivated to do so in order to use a simple method of obtaining human monoclonal antibodies, by circumventing the tedious immortalization by hybridoma formation (claim 41).

With respect to the argument that Jat et al. teach unpredictable degree of immortalization, since the ability to immortalize thymic epithelial cells varied substantially, it is noted that the paragraph Applicant's citation (which is on p. 5100, last phrase of the first full paragraph) is taken out of context. Jat et al. clearly teach that, similar to fibroblasts, thymic epithelial cells can be successfully immortalized; the difference Jat refers to the *in vivo* differential behavior of thymic epithelial cells and liver cells in that they both express similar high levels of tsSV40Tag, however, only thymic epithelial cells show abnormal growth *in vivo*; this has nothing to do with thymic epithelial cell immortalization, since Jat et al. teach successful immortalization of such cells (Abstract, p. 5097, column 2, paragraph bridging p. 5098p. 5100, column 1, first full paragraph). Moreover, Jat et al. suggest that the Immortomouse could be used to generate immortalized cell lines other fibroblasts and thymic epithelial cells (p. 5099, column 1, first full paragraph, p. 5100, column 1, last paragraph). Prior art, other than

Jat et al., also teaches successful derivatization of diverse immortalized cell lines from different organs of the Immortomouse, such as marrow-derived mesenchymal cell lines, granulosa cell lines, glial cell lines, pancreatic cell lines, or renal cell lines (see Dennis et al., Connect Tissue Res, 1996, 35: 93-99, Abstract; Walther et al, Biol Reprod, 1999, 60: 1078-1086, Abstract; Bronstein et al., J Neurochem, 1998, 70: 483-491, Abstract; Blouin et al., In Vitro Cell Dev Biol Anim, 1997, 33: 717-726, Abstract; Loghman-Adham et al., Kidney Int, 1997, 52: 229-239, Abstract; Barber et al., Biochim Biophys Acta, 1997, 1355: 191-203, Abstract). Therefore, the art teaches that diverse cell lines can be generated from the Immortomouse, and one of skill in the art would have had a good reason to believe that immortalized splenocytes could also be obtained, especially that all nucleated cells in the Immortomouse comprise tsSV40Tag in their genome.

The argument that one of skill in the art would not have been expected to have a reasonable expectation of success in achieving the claimed invention is not found persuasive because **(i)** crossing two genetically modified mice and select for offspring containing the genetic elements from both was routine in the art at the time the invention was made and **(ii)** the art teaches that antibody-producing cells can be successfully immortalized by diverse methods, such as hybridoma formation or transformation with SV40Tag.

With respect to the submitted declaration and the selective overgrowth of specific antibody-secreting cells as opposed to the non-secreting cells, it is noted that Applicant just observed an inherent property of the splenocytes isolated from the cross between the Immortomouse and the Xenomouse; by using the method according to the

teachings above (i.e., obtaining a cross between the Immortomouse and the Xenomouse), one of skill in the art would have necessarily obtained the spelnocytes with similar properties. Moreover, the result is not surprising, since the same phenomenon is observed with immortalization via hybridoma formation, wherein there is a selection for the blasting B cells that arise as a result of immunization with the antigen of interest. This is exactly what the first reviewer is saying. The first reviewer is also saying that the results are surprising just because he did not believe Applicant's conclusion that all splenocytes secreted antibodies directed toward the immunizing antigen; in his opinion, obtaining 58% positive clones is explained by selective overgrowth of specific antibody-forming blasting B cells obtained as a result of immunization with the antigen, which is similar to what happens with hybridoma. Therefore, one of skill in the art would have had a reasonable expectation of success in cloning the splenocytes of interest, without being concerned with the non-secreting splenocytes taking over the culture. The declaration also provides the opinion of a second reviewer, who states that phages (i.e., the antigen used by Applicant) are very immunogenic and observes that Applicant used large amounts of phages to immunize the mice. Because of this, the second reviewer states that the apparent ease of obtaining a large number of clones would not apply to the most of the antigens, which are much less immunogenic and these cases screening for clones of interest would be as time consuming and expensive as it is for hybridoma. Applicant did not provide any evidence that the results obtained with phages are replicated for immunogens that are

weaker than phages, which are the majority of the antigens. In conclusion, the assertion of unexpected results is not found persuasive and the rejection is maintained.

New Rejections/Objections

Claim Objections

6. Claims 26, 35, 37, and 38 are objected to under 37 CFR 1.75(c) as being in improper form because they are dependent from the following claim 40. Correction is required.

Conclusion

6. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Noble et al. (Transgenic Research, 1995, 4: 215-225, Abstract) was cited to cited to evidence that the prior art suggests crossing Immoromouse with tgenetically modified mice of interest.

Dennis et al. (Connect Tissue Res, 1996, 35: 93-99, Abstract), Walther et al. (Biol Reprod, 1999, 60: 1078-1086, Abstract), Bronstein et al. (J Neurochem, 1998, 70: 483-491, Abstract), Blouin et al. (In Vitro Cell Dev Biol Anim, 1997, 33: 717-726, Abstract) Loghman-Adham et al. (Kidney Int, 1997, 52: 229-239, Abstract), Barber et al. (Biochim Biophys Acta, 1997, 1355: 191-203, Abstract) were cited to evidence that one of skill in the art would have had a reasonable expectation of success in obtaining

diverse cell lines from an Immortomouse or from a cross between the Immortomouse and xenomouse.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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